

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,600

Open access books available

137,000

International authors and editors

170M

Downloads

Our authors are among the

154

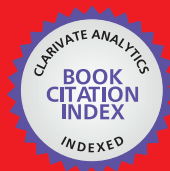
Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Retrospective, Perspective and Prospective of B-Complex Vitamins: Encapsulation of Vitamins and Release from Vitamin-Loaded Polymers

*Fatma Nur Parin*

## Abstract

Vitamins are regarded as vital nutrients because, when combined, they performed hundreds of functions in the body. They strengthen bones, heal wounds, and boost your immune system. In addition, they transform food into energy and heal cellular damage. In this regard, B-complex vitamins, such as thiamine, riboflavin, and niacin are soluble vitamins that serve as coenzymes in energy metabolism enzymatic activities which building blocks of a healthy body. However, B-complex vitamins are sensitive to light, pH conditions, and temperature. Consequently, they must be encapsulated before they may be used in pharmaceuticals. Recently, it is mainly focused on reducing drug degradation or loss, increase drug bioavailability, limit adverse effects, and improve drug accumulation in the targeted location. To maintain optimum bioavailability during a defined term of therapy, the fraction of drug dosage released from a controlled release product must be significant enough to adjust for the quantity of active drug metabolized and/or eliminated from the body over the same period. Drug release systems also aim to increase the effectiveness of the drug and treat the damaged area. In this chapter, it is aimed to study the production of the vitamin-loaded polymer systems in various forms, such as micro/nanoparticles, micelle, hydrogel, liposome, and nanofiber, as well as release studies in pharmaceutical and biomedical applications.

**Keywords:** encapsulation, vitamin release, vitamin-loaded polymer, B-complex vitamins, nutrients

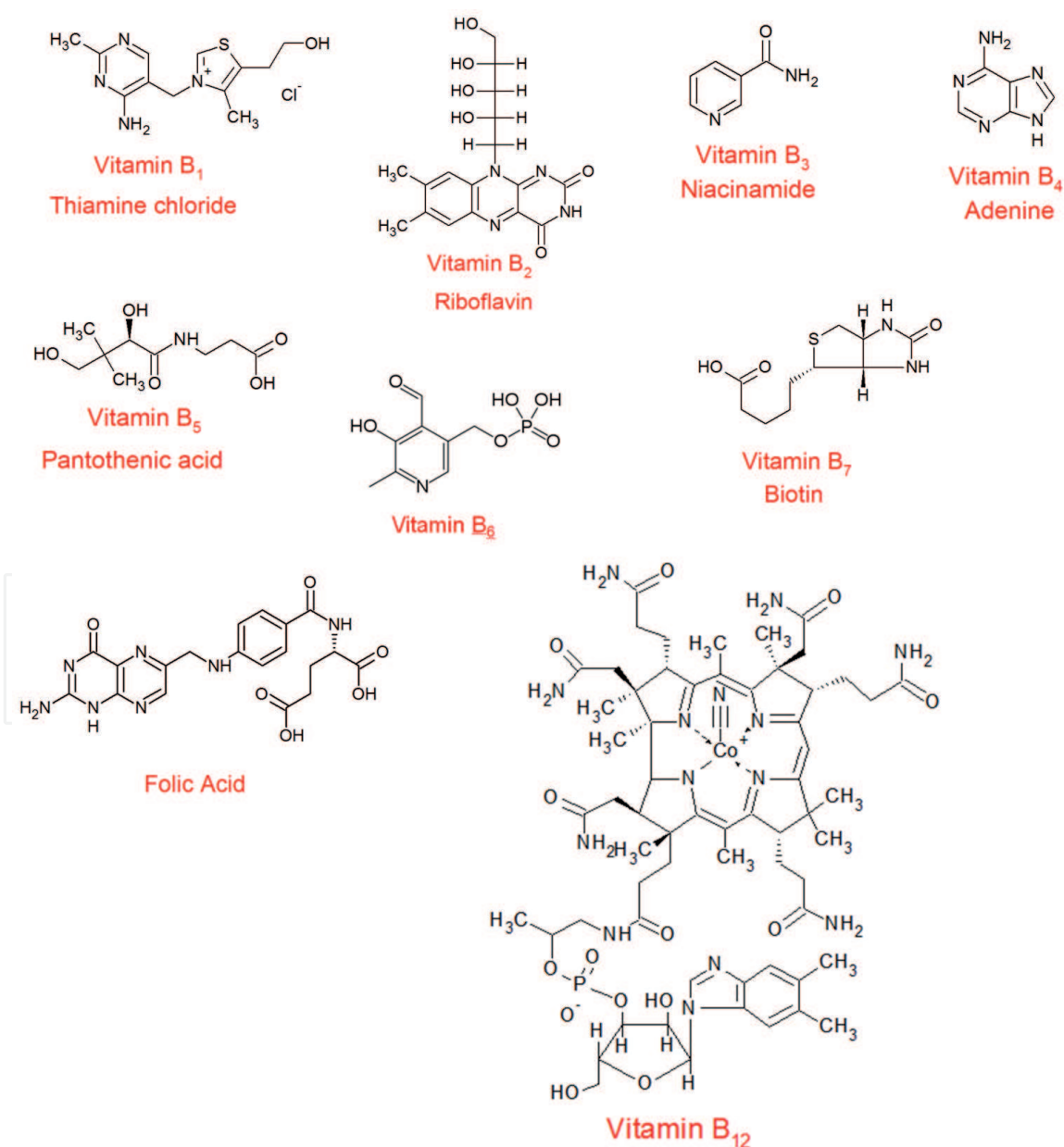
## 1. Introduction

Vitamins are a category of chemical substances that are not synthesized naturally by the body and therefore must be supplied in small amounts from food. The B-vitamins are a group of eight water-soluble vitamins that play important, interconnected functions in cellular activity, acting as co-enzymes in a wide range of catabolic and anabolic enzymatic processes [1]. Thiamine (B<sub>1</sub>), riboflavin (B<sub>2</sub>), niacin (B<sub>3</sub>, also known as nicotinamide or nicotinic acid amide), pantothenic acid (B<sub>5</sub>), pyridoxine (B<sub>6</sub>), biotin (B<sub>7</sub>), folic acid or folate (B<sub>9</sub>), and cobalamin are the

B vitamins ( $B_{12}$ ) [2]. Their combined effects are especially significant in many areas of brain function, including energy generation, DNA/RNA synthesis/repair, genomic and non-genomic methylation, and the formation of various neurochemicals and signaling molecules [3]. B-complex vitamins are known as energy vitamins and stress fighters. Furthermore, the B-Complex vitamins are usually referred to as “beauty vitamins” since they are necessary for healthy hair, skin, and nails.

Polymeric materials have been regarded as the most effective drug delivery vehicles due to their superior pharmacokinetic characteristics. Several new drug delivery methods have been suggested with the rapid advances of nanotechnology. Polymeric drug delivery is described as a formulation or a technology that allows a therapeutic material to be introduced into the body. The nano-sized drug delivery system, in particular, can be built to overcome the current limitations of some drugs, such as poor bioavailability and significant cytotoxic side effects.

Polymers combined with B-complex vitamins can be bioactive to offer therapeutic effect on their own, or biodegradable, to enhance release kinetics and reduce carrier aggregation. Thus, B-vitamins encapsulated with polymer are protected



**Figure 1.**  
Chemical structure of the B-complex vitamins.

from degradation caused by environmental effects. Several natural polymers, such as chitosan, starch, dextran, albumin, gelatin, alginate, gums, and also synthetic polymers, such as polylactic acid (PLA), poly-(lactide-co-glycolide) (PLGA), polyanhydrides, and polycaprolactone (PCL), have been utilized in the therapeutic delivery systems [4]. The majority of vitamin B-complex delivery of polymers can be broadly classified as hydrogels, films, nanofibers, beads or micro/nanoparticles, and polymer-drug conjugates, which are discussed in further detail in later sections.

This chapter explains polymer-based materials containing B-complex vitamins briefly and reviews studies in food, biomedical, drug delivery, tissue engineering, wound dressing, cosmetics, and other applications. The importance of vitamin-loaded polymers with unique features in different forms such as outstanding, pH and thermal sensitivity, bioactivity, swelling character, controlled release behavior, biodegradability, good *in vitro* and *in vivo* biocompatibility, and so on is discussed in detail. Finally, future problems and several ideas regarding the production of vitamin-loaded polymers as well as commercial applications have been highlighted (Figure 1).

## 2. Vitamin-loaded polymers

Liposomes, sponges, foams, micro/nanoparticles, fibers, hydrogels, and emulsions have been developed to increase pharmaceutical absorption, stability, penetration, half-life, and bioavailability [5, 6]. From this point, vitamin-loaded polymers have been encapsulated via different techniques such as layer by layer, solvent casting, spray drying, electrospinning/electrospraying, freeze-drying, emulsion polymerization, and complex coacervation. In this regard, vitamin B-complex is encapsulated in different forms with various polymer combinations, enhancing their controlled release and bioavailability. The following sections describe the many applications of vitamin B-complex-releasing polymer forms.

### 2.1 Hydrogels

Superabsorbent polymers (SAPs) or hydrogels are three-dimensional cross-linked networks of hydrophilic polymers (3D) that can absorb and retain a substantial proportion of liquid (>20%) within their weight [7, 8]. Hydrogels can be used to encapsulate medicines while still preserving bioactivity during gelation and release. Injectable methods can ensure that these medicines are administered locally to the location of the lesion in a continuous and controlled approach.

Natural polymers (e.g., sodium alginate, carboxymethyl cellulose, cellulose, chitosan, gelatin, pectin, starch), synthetic polymers (polyacrylamide, polyacrylic acid, polymethacrylic acid, polyethylene glycol, polyvinyl alcohol), and different acrylates can all be utilized to construct 3D networks [9]. The main factors involved in reversible swelling are based on chemical interactions and physical contact.

There have been several attempts to mix B-complex vitamins with hydrogels for use in medical applications. In this scope, Liu et al. [10] prepared B<sub>12</sub> vitamin-loaded smart magnetic hydrogels to be utilized in bio-separation, and drug carrier applications. In their study, gelatin has been used as a matrix and Fe<sub>3</sub>O<sub>4</sub> nanoparticles are used as magnetic agents. *In vitro* test results showed the crosslinked density of the hybrid gel affected porosity, pore size, and B<sub>12</sub> release profile, as well. According to UV-VIS analysis, the increased crosslinking of the gelatin matrix via genipin crosslinker led to more vitamin B<sub>12</sub> absorption at 361 nm [10].



Bajpai and Dubey [11] synthesized VB<sub>12</sub>-loaded poly(N-vinyl-2-pyrrolidone-co-acrylic acid) hydrogels and evaluated swelling and *in vitro* release behavior. It has been reported pH conditions influence the gel swelling and controlled release profile of vitamins. The gels exhibited nearly  $47.8 \pm 4.9\%$  swelling in the medium of pH 1.2, while nearly  $2164.6 \pm 21.8\%$  swelling was observed in the phosphate buffer medium of pH 6.8 due to the functional COO<sup>-</sup> groups in acrylic acid [11].

Gong et al. [12] engineered poly(ethylene glycol)-poly( $\epsilon$ -caprolactone)-poly(ethylene glycol) (PEG-PCL-PEG) and Pluronic F127 copolymer via sol-gel transition to utilized in biomedical applications as injectable *in situ* gel-forming drug carrier. Because of its high water solubility, VB<sub>12</sub> was rapidly released from the composite hydrogel. The release results showed that VB<sub>12</sub> release slowed down due to an increased amount of hydrogel, and there was a 10% decrease in total release with an increased amount of VB<sub>12</sub> in the hydrogel. The higher Pluronic F127 content caused the higher VB<sub>12</sub> release amount. Furthermore, cell viability tests revealed that the obtained composite hydrogel copolymers were biocompatible and had low cell cytotoxicity [12].

Ozey [13] synthesized the biocompatible poly(2-hydroxyethyl methacrylate-co-N-allylsuccinamic acid)/B<sub>12</sub> vitamin hydrogels. *In-vitro* release study indicated around the total release of B<sub>12</sub> vitamin has 96.9%, 95.8%, and 93.7% release amount in three different media (pH 1.2, PBS and NaCl isotonic serum). As a result, different release media have been found to partially effect the B<sub>12</sub> release profile. However, it has not seriously affected the total release amount [13].

In a similar study, Maheswari et al. [14] synthesized poly(N-isopropylacrylamide-co-N-vinyl-2-pyrrolidionone) with B<sub>12</sub> vitamin via radical polymerization. In this study, increased N-vinyl-2-pyrrolidionone (NVP) concentration had led to an increase in pore structure and interconnectivity with pores. The swelling ratio changed with temperature due to using thermo-responsive N-isopropyl-acrylamide (NIPA) monomer. The composite hydrogel had 85% VB<sub>12</sub> release at 30°C for 10 h. In last, the kinetic results showed the VB<sub>12</sub>-loaded polymer templates had a non-Fickian diffusion mechanism [14].

Nath et al. [15] developed gelatin-g-poly(acrylic acid-co-acrylamide)/montmorillonite (MMT) clay composite hydrogel containing B<sub>12</sub> vitamin and they investigated the utility of these materials in pH-responsive drug delivery systems. It was observed that the vitamin B<sub>12</sub> released from the hybrid hydrogels with 40% (in pH 1.2) and 80% (in pH 7.4) of release amount over 6 h, respectively. Moreover, in comparison to the neat hydrogel, the biodegradability of the vitamin-loaded increased. All samples had no cytotoxicity effects [15]. Another study of the same research group is about pH- responsive controlled VB<sub>12</sub> release. It was found almost 50% and 70% VB<sub>12</sub> were released in two different pH media (1.2 and 7.4) from the hydrogels for 48 h [16]. Fast VB<sub>12</sub> diffusion was reported in artificial intestinal fluid (AIF, pH 1.2) indicating the pH-dependent cumulative release percentage of VB<sub>12</sub>. This phenomenon is due to the protonation of a higher number of carboxylic acid (-COOH) groups in VB<sub>12</sub> at a pH of 7.4. It was revealed to influence the degree of gel swelling, which enhances VB<sub>12</sub> release, as well as an increase in electrostatic repulsion between the increased amount of ionized -COOH and -OH groups, which leads to increased space expansion inside the network structure.

CMC-xylan/VB<sub>12</sub> hydrogels had been prepared in different molar ratios by Kundu and Banerjee [17]. According to in-vitro studies, the composite gels indicated a minimum cumulative VB<sub>12</sub> release of 28% in pH 1.2. Moreover, 88% in pH 6.8 and 98 in pH 7.4 media, respectively.

Another study contributed to the development of VB<sub>12</sub> loaded-alginate (Alg) scaffolds by the microfluidic method [18]. In this study, alginate and CaCl<sub>2</sub> are used as a template of vitamin, and crosslinker, respectively. The vitamin-loaded hydrogel

scaffolds in various alginate concentrations indicated a zero-order kinetic model with more than 80% drug release in 4.5 h.

Gum arabic cross-linked PVA/FA hydrogels were also reported to be a drug delivery carrier with high blood compatibility, good porosity, pH sensitivity and high mechanical properties [19]. The crosslinked hydrogels had a higher swelling ratio at higher pH. Further, *in vitro* release tests indicated the optimized hydrogel had the release FA amount of 78% and 32% at pH 7.4 and 2.1, respectively. It was found the PVA-based hydrogels prevent FA from UV degradation, and therefore, researchers evaluated the hydrogels could be UV-photoprotect material.

In topical/transdermal drug release, active substances have advantages such as localized at the site of infection and reducing their systemic effects [20]. Jung et al. [21] reported that liposomal hydrogels containing VB<sub>12</sub> could be a candidate for the treatment of atopic dermatitis. VB<sub>12</sub> derivative adenosyl cobalamin (AdCbl) was loaded into liposomes via a filmhydration method. The results showed the liposomal hydrogels have between 11.5–38.8% loading efficiency of AdCbl. The permeability tests also demonstrated liposomal gel form of AdCbl had 17 times more permeability than in only gel form of AdCbl after 24 h. Consequently, as AdCbl-loaded liposome structures were used, the release amount significantly increased [21].

Folic acid (C<sub>19</sub>H<sub>19</sub>N<sub>7</sub>O<sub>6</sub>) is an important member of the B-complex vitamin which also known as vitamin B<sub>9</sub>. It consists of the conjugation of one or more L-glutamate units of 4-((pteridine-6-methyl)-amino) benzoic acid [22]. Besides, folic acid is an important factor in the physiological processes of cell metabolism; it is a coenzyme involved in cell growth and development, DNA synthesis and repair, and many metabolic reactions [23].

Folates in their reduced state (without glutamic acid) are chemically unstable and expose oxidatively breakdown at the C-9 and N-10 bonds, resulting in substituted pteridine and p-amino benzoyl glutamate (PABA) moieties. Camacho et al. [24] studied encapsulation of folic acid in copper-alginate hydrogels. This organometallic hydrogels performed as a gastro-resistant material, and slow folic acid release occurred only at pH > 5, particularly under simulated intestinal media (pH 8.2). Besides, the successful materials showed more release in alkaline media (>80 ppm) compared to acidic media (pH 5.4) (~8 ppm) with a zero-order kinetic model [24].

Moreover, in certain commercially available compounds, such as Fruit & Passion Boutiques Inc.'s Hydro Gel Face Masks, the moisturizing effect of these organic polymeric gels is combined with more complex drug-delivery systems designed to release biomolecules such as vitamin C or B<sub>3</sub> [25].

## 2.2 Films

The film is commonly used in food packaging applications. The edible films and edible coatings are usually used similarly in this field, however, they differ in preparation form [26]. Edible films are formed initially like a solid sheet and then applied to the product surface or between food components, whereas edible coatings are produced directly onto food surfaces once the product makes contact with them. These films and coatings are usually utilized to provide extra barrier protection to increase the shelf life of the food product [27]. Meanwhile, they can also be engineered as vitamin carriers. In this regard to biomaterials, where biopolymers are important due to their biodegradability and biocompatibility, particularly with free-standing devices for wound dressing applications. Coating and film coating are frequently used in applications involving bone implants, cardiovascular devices, wound control and treatment, and oral dissolving strips, as well.

van Dijkhuizen-Radersma et al. [28] have reported polymer composition and crystallinity directly affect the drug release behavior. In the study, VB<sub>12</sub>-loaded poly(ethylene glycol)/poly(butylene terephthalate) films were synthesized by emulsion polymerization. The release rates and amounts of the resulting films vary between 20% and 100% depending on the copolymer ratios used. Moreover, they determined the total release of VB<sub>12</sub> from the films with 50–100 µm in one day and a sustained release for more than 12 weeks [28].

In recent decades, the importance of thin films in biology and biomaterials research has increased rapidly. Thin films can be coated on a variety of surfaces depends on their physicochemical properties such as wettability, reactivity, conductivity, and corrosion resistance. Thin films are currently being used in the fields of tissue engineering and biomedical industries for osseointegration in dental and orthopedic implants, biodegradable/biobased scaffolds, and biomimetic materials [29]. In this context, Mallakpour and Hatami [30] prepared chitosan nanocomposite films containing folic acid to utilize in tissue engineering as bone and teeth additives. Contact angle measurements showed that the produced films had improved wettability and were more hydrophilic. Furthermore, the bioactivity of these NC films by soaking them in simulated bodily fluid (SBF, pH 7.4), and the pH changes for this solution were observed for 1 month [30].

Banerjee and Ganguly [31] studied on encapsulation of VB<sub>12</sub> in layered biocomposite films to use in drug delivery, wound healing, and tissue repair applications [31]. In this study, alginate and chitosan was prepared by freeze-dry method as inner and outer layers, respectively. The macrovoids were formed by gas bubbles. Although lyophilized composite films have a high absorption capacity, this form of structure dissolves fast in releasing media. SEM images exhibited the bubbles were homogeneous, having a diameter of almost 0.5 mm, and bubbles were also obtained in multiple layers. Two polymer gel substrates were thought to be different, but the release test showed the diffusivity of biocomposite solute is much lower in crosslinked chitosan than in calcium alginate. In addition, the voids in films did not affect drug release behavior but affect the release amount of drug. Films with void have been found to release more drugs than non-void films.

Orodispersible Film (ODF) is a new progressive dosage form that can provide patients with excellent drug delivery benefits. They are the most revolutionary alternative to conventional dosage forms like pills and capsules [32]. Among all oral drug delivery methods, Oral Film Technology (OFT) has attracted a lot of interest. This dosage form is also known as rapid dissolving film, fast-dissolving film, and orodispersible film [33]. In this scope, Suryawanshi et al. [34] fabricated cyanocobalamin-loaded orodispersible films via a hot-melt extrusion process [34]. The choice of polymer for this process is an important step in the development of ODFs. In this study, Soluplus® (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer) was utilized as a solvent for drugs that were insoluble in water. Morphological analysis showed the surface of the cyanocobalamin-loaded films was smooth and homogeneous. Besides, 3D micrographs of the film surfaces had a uniform structure. The resulting VB<sub>12</sub> loaded-films have thickness values varied from  $0.21 \pm 0.02$  to  $0.33 \pm 0.03$  mm. However, the thicknesses of optimized film  $0.24 \pm 0.02$ . The average tensile strength of VB<sub>12</sub> films ranged from  $1.53 \pm 0.84$  to  $15.75 \pm 0.47$  N/cm<sup>2</sup>, The optimized film's tensile strength was measured  $15.45 \pm 0.32$  N/cm<sup>2</sup>. Contact angle measurement confirmed the optimized films had superior wettability with 24.21°. Moreover, the optimized films have the amount of 99% cyanocobalamin release for 10 hour period.

PVA is a hydrophilic-based synthetic polymer [35]. It includes a carbon chain backbone with hydroxyl groups (-OH); these OH groups can act as a source of hydrogen bonding and therefore assist in the production of polymer composites [36].



Because of its biodegradability, non-toxicity, good film-forming ability, water processability, quick availability, and low cost, PVA is one of the most commonly biodegradable polymers used for different fields of industry [37]. Furthermore, the fabrication of inorganic nanoparticles in polymer matrices has attracted a great deal of interest. Especially, vitamins are used as a biocompatible modifier to form more functional groups on the surfaces of nanoparticles. Many studies on polymer-based metal oxide nanocomposites have been conducted. In this respect, Mallakpour and Shafiee synthesized  $\text{ZrO}_2/\text{PVC}$  nanocomposite films via the solvent casting method [38]. Vitamin  $\text{B}_1$  (thiamin) has been used as a ligand for  $\text{ZrO}_2$  NPs due to the many functional groups such as amino and hydroxyl groups. The results showed  $\text{VB}_1$  is an excellent bioactive agent which provides good dispersion and enhances the interface between NPs and polymer matrix. The modification increased both the surface area of NPs and prevent the formation of zirconium aggregates in films. TEM analysis showed the particle size of  $\text{ZrO}_2\text{-VB}_1$  NPs has around 36 nm. UV-Vis spectrum revealed that NC films more UV absorption than neat PVC films. The modification did not influence on the crystalline structure of  $\text{ZrO}_2$ , according to the XRD analysis. Moreover, mechanical testing demonstrated that NC films were more flexible than neat PVC ones. As a result, adding these NPs to hydrophobic materials like PVC increases surface free energy while decreasing contact angle.

In a similar study, Mallakpour and Mansourzadeh fabricated PVA films including CuO nanoparticles modified with vitamin  $\text{B}_1$  (thiamine) [39]. In the study, thiamine improved polymer-metal compatibility by creating active regions on the surfaces of metal particles. FTIR analysis showed the new peaks were formed in CuO NPs. The addition of NPs to the PVA matrix further enhanced the optical and mechanical properties.

Buccal delivery has been studied as an alternative to traditional oral delivery for several drugs with limited oral bioavailability. The buccal route also offers the benefit of low enzymatic activity and acceptability by certain sensitizers [40]. The buccal route for drug delivery has received a lot of attention to solve the problem of pre-systemic metabolism caused by gastrointestinal degradation and first pass metabolism [41]. Buccal mucosa has a higher blood supply and is more permeable than oral mucosa. Mohamad et al. [42] designed chitosan/PVA containing  $\text{VB}_{12}$  buccal hydrogel films. Vitamin-polymer interactions are confirmed by FTIR analysis [42]. According to SEM images, all film samples had homogenous structures without drug agglomeration. In general, the obtained film formulations demonstrated fast drug release due to water absorption by the hydrophilic-based polymers, chitosan, and PVA, which improved wetting, swelling, and penetration of water into the matrix of the film, and therefore increasing drug diffusion phenomena. At the end of 40 minutes, the amount of drug released was 98.59%. Consequently, Higuchi kinetic model has been determined to be the best model for drug release kinetics for films.

Thiamine hydrochloride (THCl) and nicotinic acid (NA)-loaded propylene-glycol (PG) buccal films have been developed using a two-dimensional (2D) inkjet printing method [43]. The rough surface and formation of a pore network in the films were revealed by SEM images. The in vitro release tests revealed that both vitamins were released in a burst in 10 minutes. Additionally, 85%, 98%, and 100% THCl and 78%, 85%, and 100% NA are released from the 1, 5, and 9 print film in 7.5 minutes. The profiles of all formulations for both THCL and NA release were better suited to the first-order kinetic model, with the highest  $R^2$  values.

Acevedo-Fani et al. developed folic acid/polysaccharide-based nanolaminate films [44]. The topology of the nanolaminates improved as folic acid was added, resulting in a uniform and smooth layers. After 7 hours, only 22% of the FA was released from the films at pH 3, however, almost 100% of FA was released at pH 7. This is related



to be entrapped folic acid in nanolaminates due to its poor dissolution in an acidic environment. Although researchers have utilized the highly bio-functional folic acid as a great factor for anticancer drug delivery, antibacterial agents, and fluorescence endoscopic detection, there are also studies for usage in electronic applications. Apart from the studies, folic acid has been used in energy storage applications [45]. It was found that FA as the bio-polymeric ligand which was present in different amounts in PVDF, was an effective modifying agent. The results pointed FA particles increased the interaction of  $\beta$ -phase from PVDF's energy storage capability.

### 2.3 Nanofibers

Nanofibers play a significant role in tissue engineering and drug delivery applications due to their unique properties including low density, high specific surface area, high porosity with  $<1\ \mu\text{m}$ . Many studies on drug delivery systems indicated nanofibers can be a robust carrier system for therapeutics among other types of nanocarrier systems like hydrogels, beads, films, or others owing to high drug-loading ability, high encapsulation efficiency, target-specific, sustained drug delivery, and ease of processing [46].

Drug release systems are mainly concerned with minimizing drug degradation or loss, enhancing drug bioavailability, avoiding adverse effects, and improving drug accumulation in the targeted site [47]. It is expected to improve the drug's efficacy and treat the damaged site.

A study on increasing the bioavailability of folic acid was conducted by Fonseca et al. [48]. In the study, starch was used as a matrix, and the morphology and release behavior of nanofibers containing varying amounts of FA (5, 10, and 15%) were investigated. Although the diameters of nanofibers formed below 100 nm did not change substantially, it was observed some beads in FA-loaded fibers (5%) higher than in other samples. Moreover, TGA and UV-A radiation results have shown that starch is an effective matrix for FA encapsulation.

Evangelho et al. used an electrospray method to create vitamin B<sub>9</sub>-loaded zein nanofibers and vitamin B<sub>9</sub>-loaded zein capsules [49]. In the study, thermal and radiation resistance of the VB<sub>9</sub> to determine its availability in food applications. According to SEM micrographs, the addition of VB<sub>9</sub> did not affect on the morphology of the nanofibers and capsules; nevertheless, samples were generated at three different amounts (0.5, 1, and 1.5%, w/w) changed the fiber and capsule diameters. VB<sub>9</sub>-loaded zein nanofibers exposed to UV-A radiation for 1 and 24 hours shown significant resistance compared to non-exposed nanofibers. Zein capsules containing 1% VB<sub>9</sub> were also found to be resistant to UV-A. As the mentioned previous section, folic acid is sensitive to UV radiation due to stimulation of the bond between C<sub>9</sub> and N<sub>10</sub> and this causes the breakdown of the bond and the production of photo-degradation products such as P aminobenzoyl-L-glutamic acid, 6-formylpterin, or 6-carboxypterin. It has been presumed that the resistance of VB<sub>9</sub> in both zein fibers and capsule structures may be related to the interaction of vitamins with amino acids in the structure of Zein protein, such as Proline, isoleucine, alanine, phenyl-alanine, methionine, valine, and leucine, and that this interaction makes it difficult to break down the C<sub>9</sub>-N<sub>10</sub> bond of folic acid. Additionally, TGA analysis revealed that pure folic acid in powdered form degrades considerably faster than folic acid in nanofiber and capsule form.

Amaranth protein/pullulan electrospun/VB<sub>9</sub> fiber structures were fabricated by Aceituno-Medina et al. [50]. The study aimed encapsulate and photoprotection of VB<sub>9</sub>, a model bioactive molecule. It has been suggested that the photostability of VB<sub>9</sub> in nanofibers may have better than that produced capsules via conventional

techniques such as ionic gelation, coacervation, and spray drying. Optical and electron microscope results showed that VB<sub>9</sub> causes an increase in viscosity, resulting in thicker fibers. VB<sub>9</sub> was extracted from electrospun fibers using PBS for UV-Vis analysis. After UV exposure of non-encapsulated pure VB<sub>9</sub>, some changes have occurred in the UV-Vis spectrum, and some characteristic UV absorption peaks of VB<sub>9</sub> are broken down into shorter peaks. It has been associated with p-aminobenzoic acid (PGA) and 6-formylpterine (FPT), which are the degradation products of peaks at 275, 278, 310 and 365 nm, relatively.

Some efforts also performed in the incorporation of VB<sub>9</sub> and modified PVA-polyethyleneimine electrospun fibers to use in electronic applications as cancer diagnosis and treatment [51]. The same group prepared polydopamine-VB<sub>9</sub> complexes and the morphological structures of the obtained nanofibers due to the interactions between the polymer and bioactive material. The morphological structures of nanofibers produced by preparing polydopamine-folic acid complexes are predicted to use as graphene-like structures in energy applications such as organic semiconductor material due to  $\pi$ - $\pi$  interactions formed between the polymer and bioactive material [52]. The same research group also developed multifunctional folic acid-functionalized dendrimers onto electrospun cellulose acetate nanofibers for the specific capture of cancer cells [53].

Other nanofibrous structures based on PVP/dextran octadecyl amine/montmorillonite/VB<sub>9</sub> conjugates have been fabricated by Şimşek et al. [54]. The cytotoxicity results of nanofibers revealed that VB<sub>9</sub> has no negative effect on Vero cells (liver cells), and these fibers could be a pioneer for cancer studies and tissue engineering applications. The electrical properties of the functional nanofibers composed of dextran, PVP, and VB<sub>9</sub> were also investigated by the same study group [55]. As a result, amorphous structures of lower crystallinity and colloidal form of polymer mixtures tend to form the intermolecular hydrogen bond.

Hydrophilic drugs might cause a rapid burst release in the PBS buffer or in vivo conditions due to their high solubility [56]. Madhaiyan et al. prepared cyanocobalamine (vitamin B<sub>12</sub>)-loaded biocompatible PCL nanofibers and carried out plasma treated to nanofibers for periods of 5, 20, 40, and 60 seconds [57]. Contact angle measurements revealed a decrease in surface hydrophilicity from 139° to 108° due to the hydrophilic nature of VB<sub>12</sub>. Unmodified nanofibers exhibited 18% sudden release in the first 4 hours in the PBS environment and 39% release after 48 hours. Moreover, modified nanofibers with a period of 60 seconds had the highest release value, with a total rate of 95%.

Soy proteins have been used to develop biodegradable and biocompatible nanofibers containing rhodamine B and riboflavin in order to study controlled drug release and desorption processes [58].

Llorens et al. prepared polylactic acid (PLA) nanofibers containing vitamin B<sub>6</sub> and evaluated their release in a hydrophilic Sørensen-ethanol release media and a hydrophobic Tris/Borate/EDTA (TBE) release medium [59]. It was found that within the first 8 hours in the TBE environment, the drug was released quickly from nanofibers; however, in the hydrophilic environment, the drug was released slowly and sustain behavior for several days. From the SEM micrographs, some aggregates formed in PLA nanofibers were related to the presence of vitamin B<sub>6</sub> crystals. As vitamin loading increases, nanofiber diameters increase from 921 nm to 1013 nm, and porosity increases from 69–85%. Cell proliferation results have also shown that these nanofibers have a high antioxidant activity which were produced against free radicals that cause cell damage.

Agarwal et al. produced films with cellulose acetate nanofibers containing nano-ZnO, vitamins B<sub>2</sub> and C for use in oral applications [60]. According to UV-Vis

analysis, the release amount of vitamins B<sub>2</sub> and C from nanofibers were measured to be 25% and 95%, respectively. It has been observed that vitamin B<sub>2</sub> is stable in the environment, while vitamin C has a reversible reaction to dehydroascorbic acid and then oxidized to 2,3-diketo-L-gulonic acid via irreversible reaction. Consequently, the study pointed out that cellulose acetate can be used as a carrier in the use of vitamin B<sub>2</sub>, which is important for skin disorders, and vitamin C, which supports collagen formation.

Solar UV radiation is the major cause of skin damage owing to the production of reactive oxygen species (ROS), which causes skin collagen imperfection, roughness, allergies, and, therefore, premature aging [61]. Topical formulations have lately attracted great attention as a drug delivery system to the human skin. One approach to combating skin aging is to apply herbal phenolics and antioxidants to the skin. Folic acid (FA) is a significant antioxidant-rich B-complex vitamin that aids in the formation of healthy skin cells [62]. The utilization of folic acid as a beauty patch has been investigated by spraying it onto nanofiber surfaces. However, PVA-based polymers reduced the slow release of folic acid, allowing the process to be completed in a short time. In addition, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and neutral red uptake (NRU) assays in L929 have indicated that FA has 120% and 109% cell growth [63]. In a similar study, FA has been directly blended with hydrophilic polymers (PVA, PVP, and gelatin). Micron-sized VB<sub>9</sub> combinations have been created by the electrospraying method for topical applications. The total vitamin release percentages in different polymer matrix including PVA/FA, gelatin/FA, and PVP/FA fibers were 86.88%, 80.20%, and 76.66%, respectively [64].

Vitamin B<sub>2</sub> (riboflavin) is essential for normal reproduction, cell growth and repair, and tissue formation. Furthermore, the vitamin is used by the body to maintain tissues healthy and to repair wounds. The VB<sub>2</sub> (riboflavin)-loaded PCL/gelatin-loaded electrospun fibers have been fabricated to use in biomedical applications [65]. From the same perspective, Heydari et al. [66] developed hydrophobic peracetyl-cyclodextrin (AcCDP) nanofibers containing Vitamin B<sub>2</sub>. As expected, the nanofibers exhibited two-phase release profiles involving burst and sustain release in two different release environments (pH 1.2 and pH 7.4). Besides, it was found that they had a 60% and 40% release, respectively, for 170 hours [66].

Vitamins are necessary for cosmetics and other purposes, and transdermal vitamin delivery systems are widely available. Nanoparticulate combinations offer nearly unlimited delivery possibilities via oral, pulmonary, transdermal, and ocular routes. Vitamins their nano-based combinations would definitely assist in tissue regeneration as well as pharmaceutical delivery [64].

## **2.4 Beads**

Microcapsules or beads produced of biopolymers are of scientific and technical interest, and they have a wide range of potential medical uses, including usage as controlled drug delivery systems. The development of stimuli-responsive microcapsules, especially those composed of biopolymers, is still in its early stages [67].

With relation to hydrogel studies, Bajpai and Tankhiwale [68] prepared vitamin-loaded multilayered polymeric beads using the complex coacervation method. Chitosan and calcium alginate was used as matrix, and VB<sub>2</sub> was used as a model drug, as well. It was found that the beads released around 54% of the drug in the first 3 hours in the artificial gastric fluid (AGF) (pH 1.0), while the remaining drug was released in the mimicking intestinal fluid of pH 7.4 in 6 hours. At last,



the concentration of alginate solution used to form the outer layer, as well as the concentration of the ionic crosslinker  $\text{CaCl}_2$ , affects the release profile [68].

Puguan et al. [69] prepared calcium alginate/ $\text{VB}_{12}$  beads using the dripping technique. In the study,  $\text{VB}_{12}$  was entrapped in polymers during the gelation process. The *in vitro* study indicated the total release of  $\text{VB}_{12}$  complete within 2 hours, and the vitamin loaded-beads had burst release in 30 min. The authors claimed the amount of calcium (crosslinker) ionic strength, and pH factors influence the kinetics of gel formation, as well as the volume and stability of the beads [69].

Vitamins are extremely sensitive, resulting in losing bioactivity during food processing, and storage. Thus, microencapsulation may be used to reduce vitamin loss, allow for a controlled release procedure, and improve their stability. Spray-drying process is versatile and generates high-quality microparticles, and it is superior to other methods in that the product quality in terms of homogenous and cheap [70].  $\text{VB}_2$  has been loaded into 3 different matrix (chitosan, modified chitosan, and sodium alginate) using spray drying method. The total amount of vitamins was released in around 120 min for microparticles produced with chitosan, 15 min for microparticles produced with alginate, and 10 min for microparticles produced with modified chitosan. SEM images and release study showed were associated with a slow release to a rougher surface. For all of the biopolymer-based microparticles with a mean diameter of almost 3  $\mu\text{m}$  were detected [71]. The same group reported to  $\text{VB}_{12}$ -chitosan microparticles have controlled release behavior in gastric conditions (pH 1.2). The highest release of  $\text{VB}_{12}$  reached in 10 min. Microstructure of the materials revealed average diameter of particles vary from 3 to 8  $\mu\text{m}$  with a smooth surface and an uniform round shape [72]. Similar to the spray drying of vitamin  $\text{B}_{12}$ /alginate beads conducted by Abubakr et al. [73]. In the study, as addition of chitosan into the alginate matrix, the release of  $\text{VB}_{12}$  slowed down. Further chitosan effect the alginate stability and decrease bead permeability. Estevinho and Rocha [74] studied the kinetic models of encapsulated  $\text{VB}_{12}$  bioactive compounds. Chitosan, modified chitosan, and also sodium alginate were utilized for capsulating matrix [74]. The findings indicated zero-order model was the best fitted for chitosan/ $\text{VB}_{12}$  particles. Recently, encapsulated the vitamins  $\text{B}_2$  and  $\text{B}_3$  into six different biopolymers performed using the spray drying method by Carlan et al. [75]. Moreover, encapsulation efficiency reached values higher than 99% for all vitamin-based microcapsules. SEM images demonstrated  $\text{VB}_2$  and  $\text{VB}_3$  particles had a varying range between 0.10–0.84  $\mu\text{m}$ . Weibull kinetic model was determined suitable model for both vitamin NPs.

The selection of appropriate wall material is critical for achieving the optimum release rate and high encapsulation efficiency of bioactive compounds during the spray drying process. It has been reported that a wall material mixture of polysaccharide-based like gum acacia, cashew nut gum, sodium alginate, sodium carboxymethyl cellulose, and Eudragit RS100 has affected the release kinetics of encapsulated vitamin  $\text{B}_{12}$  [76]. Bajaj et al. [76] used carbohydrate-based wall materials to co-encapsulate the vitamin  $\text{B}_{12}$  and  $\text{D}_3$  for the food industry. In the study, the size of smooth microcapsules ranged between 3 and 7  $\mu\text{m}$  without cracking. After the encapsulation process, both vitamins demonstrated higher stability and a change in release rate. Further, the *in vivo* studies showed the maximum concentration of  $\text{VB}_{12}$  was recorded at 240 min [77].

Madziva et al. [70] produced microcapsules containing folic acid varying in size from 300 to 650 nm with a shell material composed of alginate and pectin that may be utilized in food. It was observed that these biopolymers encapsulating the core exhibit significant stability and high encapsulation efficiency in food products for folic acid [70].



Azevedo et al. [78] encapsulated vitamin B<sub>2</sub> into alginate/chitosan matrix by pre-gelation ionotropic method and investigated release behavior in different conditions. The size of nanoparticles has around 120 nm with 56% encapsulation efficiency. The vitamin B<sub>2</sub>-loaded nanoparticles are more stable than vitamin B<sub>2</sub>-free nanoparticles for 5-week periods [78].

Vitamin compounds, including vitamin B<sub>1</sub> and B<sub>6</sub>, have been investigated for controlled drug delivery utilizing various clays to enhance encapsulation efficiency [79–81]. In recent years, gellan gum/laponite clay beads containing VB<sub>12</sub> was fabricated by the ionotropic gelation method [82]. The composite beads had a smoother and regular surface with 2.1 mm. The incorporation of laponite in the bead formulation enhanced drug encapsulation efficiency and delayed the kinetics of the drug in the gastric media. It has been suggested that laponite could be a useful addition in the production of gellan gum beads for long-term drug release.

Several VB<sub>2</sub> delivery systems for oral absorption have been developed to solve health problems [83–85]. Riboflavin delivery from ethyl-cellulose-coated barium alginate beads was reported by Bajpai and Sharma [86]. In a pH 1.2 media, the uncoated beads released faster than coated one. Stops et al. observed that calcium alginate beads had fast release VB<sub>2</sub> profile [87]. In another study, Kaygusuz et al. investigated the release of VB<sub>2</sub> from alginate-montmorillonite clay biocomposites [88]. The results showed two different crosslinkers (barium and calcium) utilized had no significant effect on drug release amount, however, barium-alginate beads were more stable than the others. Besides, the *in vitro* study indicated almost 50% VB<sub>2</sub> released from both (barium and calcium) composite beads. In brief, MMT-incorporated calcium and barium alginate beads were appropriate for VB<sub>2</sub> oral applications. The novel biomineralized alginate beads were also designed by Yang et al. [89, 100] to release VB<sub>2</sub>. In the study, aliphatic poly(urethane-amine) (PUA) provides thermal sensitivity. Therefore, the VB<sub>2</sub> release was higher at 55°C than at 37°C due to the shrinking of aliphatic PUA at its lower critical solution temperature (LCST) [89].

Carlan et al. [90] researched microencapsulation of VB<sub>1</sub> into different polymers such as carrageenan, chitosan, maltodextrin, modified chitosan, modified starch, pectin, sodium alginate, and xanthan gum. The size of beads ranged from 0.11 to 1.32 µm. The modified starch beads had VB<sub>1</sub> release in 10 min, while VB<sub>1</sub>-loaded xanthan gum had in 24 hours. The Weibull kinetic model performed the best on the experimental data [90].

## 2.5 Others

Carbon nanotubes (CNTs) are made up of micrometer-scale graphene sheets folded into nanoscale cylinders and topped with spherical fullerene [91]. CNTs have found widespread application from optoelectronics and energy storage to drug delivery and biosensor [92, 93]. In recent years, polymer nanocomposites have a worldwide focus to obtain novel polymer materials for practical applications by improving the properties of neat polymers. To improve the reinforcing effect of CNTs in polymer nanocomposites, good dispersion and effective interfacial adhesion between CNTs and the polymer matrix are required (NCs). However, it takes some effort to disperse effectively the CNTs in the composites due to  $\pi$ - $\pi$  interactions and strong van der Waals forces between the tubes that cause CNT aggregation in the composites [94]. Therefore, CNT hybrids are used to aid CNTs in disperse inside polymer matrices [95]. A research group decided to improve CNTs functionality and prevent aggregation in composites by treatment with VB<sub>1</sub> [96]. The results showed VB<sub>1</sub> is a biosafe molecule for poly(ester-imide) matrix and CNTs, and it

enhanced the morphological properties of polymeric composites. Moreover, the diameter of CNTs increased too, when compared to CNTs-COOH, indicating that a thin coating of VB<sub>1</sub> was bonded to the CNTs via strong interactions.

Cancer is currently one of the most challenging diseases to treat, and its prevalence is on the increase [97, 98]. Targeted anticancer treatments have been widely developed for the past three decades to eliminate cancer cells. Various colloidal carriers, such as lipid nanoparticles, nanofibers, and nanocapsules, nanogels, and polymer-drug conjugates have been investigated for anti-cancer treatments [99]. The application of specific nanomaterials such as CNTs, gold nanoparticles (GNPs), and graphene nanosheets have been considered in the majority of reviews in this field [100]. Due to its low cost, non-toxic, non-immunogenic, low molecular weight, and ease of modification, folic acid (FA) is one of the most widely acknowledged cancer-targeting agents among the different targeting agents. Folate receptors are commonly utilized in epithelial, ovarian, cervical, breast, lung, kidney, colorectal, and brain cancers compared to other agents and B-complex vitamins. Many approaches have been reported for the chemical conjugation of FA to a variety of therapeutic drugs and imaging agents [101]. Yang et al. [89, 100] prepared a folate-conjugated PCL-PEG copolymer to obtain hydrophobic doxorubicin (DOX)-encapsulated active targeting micelles and they combined these micelles with PVA. In conclusion, core-shell nanofibers are produced for the treatment of solid tumors [100]. A study on liver cancer treatment was conducted by Fan and co-workers (2019) [102]. In the study, doxorubicin (DOX)-loaded folic acid-polyethylene glycol- $\beta$ -cyclodextrin (FA-PEG- $\beta$ -CD) nanoparticles (NPs) synthesized and this material showed 11.9% drug loading efficiency and 95.2% encapsulation efficiency with 30–60 nm. In another study, folic acid was conjugated with curcumin-encapsulated gum arabic microcapsules in order to drug delivery it to breast cancer cells [103]. Poltavets et al. [101] synthesized docetaxel-loaded PLGA nanoparticles with a folate modification via an emulsion solvent-evaporation. The *in vitro* study revealed these nanoparticles performed non-functionalized nanoparticles and free docetaxel *in vitro* anticancer activities against HeLa cervical carcinoma cells [104].

### 3. Future insights

The use of vitamin B-loaded polymers presents a serious progress in the above-mentioned applications and ensures a positive advancement in the upcoming years. Treatments will be more effective and safer owing to the design and functionalization of the various polymeric materials. The potential applications show that the polymeric carriers will progress to a specific active substance to the point where it can be customized to best adapt to a specific component or environment. However, it is important to note that vitamin-loaded polymers have some challenges. First, the number of vitamin-loaded polymers presently accessible for use as the industrial scale is still limited, despite the fact that R&D has advanced from the micro to nano-size scale in the previous decade, exceeding expectations. Secondly, the majority of the tests were improved *in vitro* studies with promising findings, however, the conversion from *in vitro* outcomes to clinical success have been restricted. More clinical trials and data are required to properly understand the mechanism of these polymer carriers. Further, these polymer-carriers must also be biodegradable or have a high capacity to be removed outside the body to minimize accumulation, as well as being non-toxic and non-immunogenic. It is notable to highlight the effect that copolymers or polymer blends might play in adjusting or modifying interactions with the human body in order to control their *in vivo* studies.

In sum, various disadvantages or drawbacks must still be overcome by multiple efforts and focused multidisciplinary scientific collaboration in order to achieve the desired results.

#### **4. Conclusion**

Since the beginning of the 2000s, B-complex vitamins have been produced in polymeric materials. Vitamin-loaded polymeric materials have been produced in various structures, such as gel, film, bead, liposome, and fiber forms. Each of these materials containing vitamins has become interesting for many industrial applications. Vitamin-loaded polymer materials have been utilized in medical applications such as implants, additives, tissue engineering, drug carriers, wound dressing, cosmetic applications as a skin-care mask, cancer diagnostic agent, and food applications as food supplements, as well. On the other hand, bioactive polymers are available in smart electronic applications. Some studies also pointed that B vitamins are utilized to obtain nanocomposite materials by modification of certain inorganic nanoparticles. In the studies, it was aimed to increase the bioavailability of B-vitamins by incorporating them in polymers and to develop controlled release behaviors. Furthermore, as the vitamin is introduced to polymer, the morphological, biological and thermal properties of polymeric materials have improved.

#### **Conflict of interest**

The author declares no conflict of interest.

#### **Author details**

Fatma Nur Parin  
Polymer Engineering Department, Bursa Technical University, Faculty of  
Engineering and Natural Sciences, Bursa, Turkey

\*Address all correspondence to: nur.parin@btu.edu.tr

#### **IntechOpen**

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Kannan R., Vishnupriya V. Relationship Between B-vitamins and Bone Health. In Proceedings. 2021;3(1):20.
- [2] LeBlanc JG. Introductory chapter: B-group Vitamins. B group Vitamins Current Uses and Perspectives. 2018; 3-5.
- [3] Herrmann M, Peter Schmidt J, Umanskaya N, Wagner A, Taban-Shomal O, Widmann T, Colaianni G, Wildemann B, Herrmann W. The role of hyperhomocysteinemia as well as folate, vitamin B(6) and B(12) deficiencies in osteoporosis: A systematic review. Clin. Chem. Lab. Med. 2007;45:1621-1632.
- [4] Rani R, Dilbaghi N, Dhingra D, Kumar S. Optimization and evaluation of bioactive drug loaded polymeric nanoparticles for drug delivery. International Journal of Biological Macromolecules. 2015;78:173-179.
- [5] Agrahari V, Agrahari V, Mitra AK. Next generation drug delivery: circulatory cells-mediated nanotherapeutic approaches. Expert opinion on drug delivery. 2017;14(3): 285-289.
- [6] Singh MK, Varun VK, Behera BK. Cosmetotextiles: State of Art, Fibres& Textiles in Eastern Europe, 2011;19(87):27-33.
- [7] Parin FN, Yıldırım K, Terzioğlu P. Biochar loaded chitosan/gelatin/ poly(ethylene glycol) biocomposite beads: Morphological, thermal and swelling properties. Journal of Innovative Science and Engineering. 2020,4(2):56-68.
- [8] Mohammad J, Zohuriaan-Mehr, Kabiri K. Superabsorbent Polymer Materials: A Review. Iranian Polymer Journal. 2008;17(6):451-477.
- [9] Behera S, and Mahanwar PA. Superabsorbent polymers in agriculture and other applications: a review. Polymer-Plastics Technology and Materials. 2019;59(4):1-16.
- [10] Liu TY, Hu SH, Liu KH, Liu DM, Chen SY. Preparation and characterization of smart magnetic hydrogels and its use for drug release. Journal of Magnetism and Magnetic Materials. 2006;304(1):e397-e399.
- [11] Bajpai SK, and Dubey S. In-vitro dissolution studies for release of vitamin B12 from poly (N-vinyl-2-pyrrolidone-co-acrylic acid) hydrogels. Reactive and Functional Polymers. 2005;62(1): 93-104.
- [12] Gong CY, Shi S, Dong PW, Zheng XL, Fu SZ, Guo G, Quian ZY. In vitro drug release behavior from a novel thermosensitive composite hydrogel based on Pluronic F127 and poly(ethylene glycol)-poly (ε-caprolactone)-poly (ethylene glycol) copolymer. BMC Biotechnology. 2009;9(1):1-13.
- [13] Ozay O. Synthesis and characterization of novel pH-responsive poly (2-hydroxyethyl methacrylate-co-N-allylsuccinamic acid) hydrogels for drug delivery. Journal of Applied Polymer Science. 2014;131(1).
- [14] Maheswari B, JagadeeshBabu PE, Agarwal M. Role of N-vinyl-2-pyrrolidinone on the thermoresponsive behavior of PNIPAm hydrogel and its release kinetics using dye and vitamin-B12 as model drug. Journal of Biomaterials Science, Polymer Edition. 2014;25(3):269-286.
- [15] Nath J, Chowdhury A, Ali I, Dolui SK. Development of a gelatin-g-poly (acrylic acid-co-acrylamide)-montmorillonite superabsorbent hydrogels for in vitro controlled release



of vitamin B12. *Journal of Applied Polymer Science*, 2019;136(22):47596.

[16] Nath J, Saikia PP, Handique J, Gupta K, Dolui SK. Multifunctional mussel-inspired Gelatin and Tannic acid-based hydrogel with pH-controllable release of vitamin B12. *Journal of Applied Polymer Science*.2020;137(39), 49193.

[17] Kundu D, Banerjee T. Carboxymethyl cellulose–xylan hydrogel: synthesis, characterization, and in vitro release of vitamin B12. *ACS omega*. 2019;4(3), 4793-4803.

[18] Bhasarkar J, Bal D. Kinetic investigation of a controlled drug delivery system based on alginate scaffold with embedded voids. *Journal of applied biomaterials & functional materials*. 2019;17(2), 22808000 18817462.

[19] Pandit AH, Mazumdar N, Imtiyaz K, Rizvi MMA, Ahmad S. Periodate-modified gum arabic cross-linked PVA hydrogels: a promising approach toward photoprotection and sustained delivery of folic acid. *ACS omega*. 2019;4(14):16026-16036.

[20] Esentürk İ, Erdal MS, Güngör S. Electrospinning method to produce drug-loaded nanofibers for topical/transdermal drug delivery applications. *Journal of Faculty of Pharmacy of Istanbul University*. 2016;46(1): 49-69.

[21] Jung SH, Cho YS, Jun SS, Koo JS, Cheon HG, Shin BC. Topical application of liposomal cobalamin hydrogel for atopic dermatitis therapy. *Die Pharmazie-An International Journal of Pharmaceutical Sciences*. 2011;66(6): 430-435.

[22] Hamed E, Attia MS, Bassiouny K. Synthesis, Spectroscopic and Thermal Characterization of Copper(II) and Iron(III) Complexes of Folic Acid and

Their Absorption Efficiency in the Blood. 2009;979680:1-6.

[23] Parın F. Yaşlanma Geciktirici B<sub>9</sub> Vitamini içeren farklı non-woven kumaşların üretimi ve kontrollü salımının incelenmesi [thesis]. Bursa Teknik Üniversitesi ;2021.

[24] Camacho DH, Uy SJY, Cabrera MJF, Lobregas MOS, Fajardo TJMC. Encapsulation of folic acid in copper-alginate hydrogels and its slow in vitro release in physiological pH condition. *Food Research International*. 2019;119: 15-22.

[25] Chirani N, Yahia LH, Gritsch L, Motta FL, Chirani S, Farès S. History and applications of hydrogels. 2015;

[26] Falguera V, Quintero JP, Jiménez A, Muñoz JA, Ibarz A. Edible films and coatings: Structures, active functions and trends in their use. *Trends in Food Science & Technology*. 2011;22(6): 292-303.

[27] De Moraes MA, Da Silva CF, Vieira RS. Biopolymer Membranes and Films: Health, Food, Environment, and Energy Applications. Elsevier. (Eds.). (2020).

[28] Van Dijkhuizen-Radersma R, Péters FLA, Stienstra NA, Grijpma D, Feijen J, De Groot K, Bezemer J. M. Control of vitamin B12 release from poly (ethylene glycol)/poly (butylene terephthalate) multiblock copolymers. *Biomaterials*. 2002;23(6):1527-1536.

[29] Mozafari M, Ramedani A, Zhang YN, Mills DK. Thin films for tissue engineering applications. In *Thin Film Coatings for Biomaterials and Biomedical Applications*. 2016;167-195. Woodhead Publishing.

[30] Mallakpour S, Hatami M. Highly capable and cost-effective chitosan nanocomposite films containing folic acid-functionalized layered double

hydroxide and their in vitro bioactivity performance. *Materials Chemistry and Physics*. 2020;250:123044.

[31] Banerjee A, Ganguly, S. Alginate–chitosan composite hydrogel film with macrovoids in the inner layer for biomedical applications. *Journal of Applied Polymer Science*. 2019;136(22):47599.

[32] Gupta MS, Kumar TP. Characterization of orodispersible films: an overview of methods and introduction to a new disintegration test apparatus using LDR-LED sensors. *Journal of pharmaceutical sciences*. 2020;109(10):2925-2942.

[33] Gijare C, Deshpande A. Orodispersible Films: A systematic patent review. Recent patents on drug delivery & formulation. 2018;12(2):110-120.

[34] Suryawanshi D, Wavhule P, Shinde U, Kamble M, Amin P. Development, optimization and in-vivo evaluation of cyanocobalamin loaded orodispersible films using hot-melt extrusion technology: A quality by design (QbD) approach. *Journal of Drug Delivery Science and Technology*. 2021;63:102559.

[35] Parin FN, Terzioğlu P, Sicak Y, Yildirim K, ÖztürkM. Pine honey-loaded electrospun poly (vinyl alcohol)/gelatin nanofibers with antioxidant properties. *The Journal of The Textile Institute*. 2021;112(4):628-635.

[36] Divya R, Meena, M., Mahadevan, C. K., & Padma, C. M. (2014). Investigation on CuO dispersed PVA polymer films. *Journal of Engineering Research and Applications*, 4(5), 1-7.

[37] Suganthi S, Vignesh S, Sundar JK, Raj V. Fabrication of PVA polymer films with improved antibacterial activity by fine-tuning via organic acids for food packaging applications. *Applied Water Science*. 2020;10(4):1-11.

[38] Mallakpour S, ShafieeE. The synthesis of poly (vinyl chloride) nanocomposite films containing ZrO<sub>2</sub> nanoparticles modified with vitamin B1 with the aim of improving the mechanical, thermal and optical properties. *Designed monomers and polymers*. 2017;20(1):378-388.

[39] Mallakpour S, Mansourzadeh S. Application of CuO nanoparticles modified with vitamin B1 for the production of poly (vinyl alcohol)/CuO nanocomposite films with enhanced optical, thermal and mechanical properties. *Polymers for Advanced Technologies*. 2017;28(12):1823-1830.

[40] Verma S, Kumar N, Sharma PK. Buccal film: an advance technology for oral drug delivery. *AdvBiol Res*. 2014;8:260-267.

[41] Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery. *Clinical pharmacokinetics*. 2002;41(9):661-680.

[42] Mohamad SA, Sarhan HA, Abdelkader H, Mansour HF. Vitamin B12-loaded buccoadhesive films as a noninvasive supplement in vitamin b12 deficiency: in vitro evaluation and in vivo comparative study with intramuscular injection. *Journal of pharmaceutical sciences*. 2017;106(7):1849-1858.

[43] Eleftheriadis G, MonouPK, Andriotis E, Mitsouli E, Moutafidou N, Markopoulou C, FatourosD. Development and characterization of inkjet printed edible films for buccal delivery of B-complex vitamins. *Pharmaceuticals*. 2020;13(9):203.

[44] Acevedo-Fani A, Soliva-Fortuny R, Martín-BellosoO. Photo-protection and controlled release of folic acid using edible alginate/chitosan nanolaminates. *Journal of Food Engineering*. 2018;229:72-82.

[45] Roy S, Thakur P, Hoque NA, Bagchi B, Sepay N, Khatun F, Das S.

- Electroactive and high dielectric folic acid/PVDF composite film rooted simplistic organic photovoltaic self-charging energy storage cell with superior energy density and storage capability. *ACS applied materials & interfaces*. 2017;9(28):24198-24209.
- [46] Dhand C, Dwivedi N, Sriram H, Bairagi S, Rana D, Lakshminarayanan R, & Ramakrishna S. Nanofiber composites in drug delivery. In *Nanofiber Composites for Biomedical Applications*. 2017;199-223. Woodhead Publishing.
- [47] Jain KK. *Drug Delivery Systems. An Overview of Drug Delivery Systems*, USA, Springer.(2008).
- [48] Fonsecaa LM, Crizela RL, Silvaa FT, VazFontesa MR, Zavarezea ER, Guerra Dias AR. Starch nanofibers as vehicles for folic acid supplementation: thermal treatment, UVA irradiation, and in vitrosimulation of digestion, *Journal of the Science of Food and Agriculture*. (2020 <https://doi.org/10.1002/jsfa.10809>).
- [49] Evangelho JA, Crizel RL, Chaves FC, Prietto L, Pinto VZ, Miranda MZ, Dias ARG, Zavareze ER. Thermal and irradiation resistance of folic acid encapsulated in zein ultrafine fibers or nanocapsules produced by electrospinning and electrospraying, *Food Research International*. 2019;124:137-146.
- [50] Aceituno Medina, Marysol; Mendoza, Sandra; Lagarón Cabello, José María ; López-Rubio, Amparo. Development and characterization of food-grade electrospun fibers from amaranth protein and pullulan blends. *Food Research International* 54: 667-674 (2013), website: <https://digital.csic.es/handle/10261/111068>.
- [51] Fan Z, Zhao Y, Zhu X, Luo Y, Shen M, Shi X. Folic acid modified electrospunpoly(vinyl alcohol)/polyethyleneimine nanofibers for cancer cell capture applications, *Chinese Journal of Polymer Science*. 2016;34(6):755-765.
- [52] Fan H, Yu X, Liu Y, Shi Z, Liu H, Nie Z, Wu D, JinZ. Folic acid–Polydopamine Nanofibers Show Enhanced Ordered-stacking via  $\pi$ - $\pi$  Interactions, *The Royal Society of Chemistry*. 2015;11(23):4621-4629.
- [53] Zhao Y, Zhu X, Liu H, Luo Y, Wang S, Shen M, Shi X. Dendrimer-functionalized electrospun cellulose acetate nanofibers for targeted cancer cell capture applications. *Journal of Materials Chemistry B*. 2014;2(42):7384-7393.
- [54] Şimşek M, Rzayev ZMO, Bunyatova U, Khalilova S, TürkM. Multifunctional Electrospun Biocompatible Nanofiber Composites from Water Dispersion Blends of Folic Acid Conjugated PVP/Dextran/ODA-MMT Nanocomposites and Their Responses to Vero cells. *Hacettepe Journal of Biology and Chemistry*. 2016;44(4):441-450.
- [55] Rzayev ZMO, Bunyatova U, Şimnullek M. Multifunctional colloidal nanofiber composites including dextran and folic acid as electro-active platforms, *Carbohydrate Polymers*. 2017;166:83-92.
- [56] Simancas-Herbada R, Fernández-Carballido A, Aparicio-Blanco J, Slowing, K, Rubio-Retama J, López-Cabarcos E, Torres-Suárez AI. Controlled release of highly hydrophilic drugs from novel poly (Magnesium Acrylate) matrix tablets. *Pharmaceutics*. 2020;12(2):174.
- [57] Madhaiyan K, Sridhar R, Sundarrajan S, Venugopal JR, Ramakrishna S. Vitamin B12 loaded polycaprolactone nanofibers: a novel transdermal route for the water soluble energy supplement delivery,



International Journal of Pharmaceutics. 2013;444(1-2):70-76.

[58] Khansari S, Duzyer S, Sinha-Ray S, Hockenberger A, Yarin AL, Pourdeyhimi, B. Two-stage desorption-controlled release of fluorescent dye and vitamin from solution-blown and electrospun nanofiber mats containing porogens. *Molecular pharmaceutics*. (2013); 10(12):4509-4526.

[59] Llorens E, J.del Valle L, Díaz A, Casas MT, Puiggali J. Polylactide Nanofibers Loaded with Vitamin B6 and Polyphenols as Bioactive Platform for Tissue Engineering, *Macromolecular Research*. 2013;21(7):775-787.

[60] Agarwal A, Anil J, Arputharaj A, Manik B, Kartick S, Prasad S, Charlene D, Nadanathangam V. Performance Characteristics of Electrospun Cellulose Acetate Nanofiber Mat Embedded with NanoZno/ Vitamins, *International Journal of Nanotechnology and Application*. 2016;6(3);1-12.

[61] Gisondi P, Fantuzzi F, Malerba M, Girolomoni G. Folic acid in general medicine and dermatology, *Journal of Dermatological Treatment*. 2007;18(3):138-146.

[62] Parin FN, Aydemir Çİ, Taner G, Yıldırım K. Co-electrospun-electrosprayed PVA/folic acid nanofibers for transdermal drug delivery: Preparation, characterization, and in vitro cytocompatibility. *Journal of Industrial Textiles*. 2021: 1528083721997185.

[63] Parin FN, Yıldırım K. Preparation and characterisation of vitamin-loaded electrospun nanofibres as promising transdermal patches. *Fibres & Textiles in Eastern Europe*. (2021).

[64] Sridhar R, Madhaiyan K, Sundarrajan S, Góra A, Venugopal JR, Ramakrishna S. Cross-linking of protein

scaffolds for therapeutic applications: PCL nanofibers delivering riboflavin for protein cross-linking. *Journal of Materials Chemistry B*. 2014;2(12):1626-1633.

[65] Zhao Q, Li B. pH-controlled drug loading and release from biodegradable microcapsules. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2008;4(4):302-310.

[66] Heydari, A., Mehrabi, F., Shamspur, T., Sheibani, H., Mostafavi, A. (2018). Encapsulation and Controlled Release of Vitamin B2 Using Paracetyl-beta-cyclodextrin Polymer-Based Electrospun Nanofiber Scaffold, *Pharmaceutical Chemistry Journal*, 52(1), 19-25.

[67] Klinger D, Landfester K. Stimuli-responsive microgels for the loading and release of functional compounds: Fundamental concepts and applications. *Polymer*. 2012;53(23):5209-5231.

[68] Bajpai SK, Tankhiwale R. Investigation of dynamic release of vitamin B2 from calcium alginate/chitosan multilayered beads: Part II. *Reactive and Functional Polymers*. 2006;66(12):1565-1574.

[69] Puguan JMC, Yu X, Kim H. Characterization of structure, physico-chemical properties and diffusion behavior of Ca-Alginate gel beads prepared by different gelation methods. *Journal of colloid and interface science*. 2014;432:109-116.

[70] Madziva H, Kailasapathy K, Phillips M. Alginate-pectin microcapsules as a potential for folic acid delivery in foods. *Journal of Microencapsulation*. (2005);22(4):343-351.

[71] Estevinho BN, Carlan I, Blaga A, Rocha F. Soluble vitamins (vitamin B12 and vitamin C) microencapsulated with different biopolymers by a spray drying



- process. Powder Technology. 2016;289:71-78.
- [72] Carlan IC, Estevinho BN, Rocha F. Study of microencapsulation and controlled release of modified chitosan microparticles containing vitamin B12. Powder Technology. 2017;318:162-169.
- [73] Abubakr N, Jayemanne A, Audrey N, Lin SX, Chen XD Effects of encapsulation process parameters of calcium alginate beads on Vitamin B12 drug release kinetics. Asia-Pacific Journal of Chemical Engineering. 2010;5(5):804-810.
- [74] Estevinho BN, Rocha F. Kinetic models applied to soluble vitamins delivery systems prepared by spray drying. Drying Technology. 2017;35(10):1249-1257.
- [75] Carlan IC, Estevinho BN, Rocha F. Innovation and improvement in food fortification: Microencapsulation of vitamin B2 and B3 by a spray-drying method and evaluation of the simulated release profiles. Journal of Dispersion Science and Technology. 2021;1-13.
- [76] Bajaj SR, Marathe SJ, Singhal RS. Co-encapsulation of vitamins B12 and D3 using spray drying: Wall material optimization, product characterization, and release kinetics. Food Chemistry. 2021;335:127642.
- [77] Oliveira AM, Guimarães KL, Cerize N, Tunussi AS, Poço JG. Nano spray drying as an innovative technology for encapsulating hydrophilic active pharmaceutical ingredients (API). J. Nanomed. Nanotechnol. 2013;4(6).
- [78] Azevedo MA, Bourbon AI, Vicente AA, Cerqueira MA. Alginate/ chitosan nanoparticles for encapsulation and controlled release of vitamin B2. International Journal of Biological Macromolecules. 2014;71:141-146.
- [79] Joshi GV, Patel HA, Kevadiya BD, Bajaj HC. Montmorillonite intercalated with vitamin B1 as drug carrier. Applied Clay Science. 2009;45(4):248-253.
- [80] Joshi GV, Patel HA, Bajaj HC, Jasra RV. Intercalation and controlled release of vitamin B 6 from montmorillonite-vitamin B 6 hybrid. Colloid and Polymer Science. 2009;287(9):1071-1076.
- [81] Kevadiya BD, Joshi GV, Patel HA, Ingole PG, Mody HM, Bajaj HC. Montmorillonite-alginate nanocomposites as a drug delivery system: intercalation and in vitro release of vitamin B1 and vitamin B6. Journal of biomaterials applications. 2010;25(2): 161-177.
- [82] Adrover, A, Paolicelli P, Petralito S, Di Muzio L, Trilli, J, Cesa S, Casadei MA. Gellan gum/laponite beads for the modified release of drugs: Experimental and modeling study of gastrointestinal release. Pharmaceutics. 2019;11(4):187.
- [83] Bajpai SK, Saxena S. Dynamic release of riboflavin from a starch-based semi IPN via partial enzymatic degradation: part II. Reactive and Functional Polymers. 2004;61(1):115-129.
- [84] Yao H, Xu L, Han F, Che X, Dong Y, Wei M, Li S. A novel riboflavin gastro-mucoadhesive delivery system based on ion-exchange fiber. International journal of pharmaceutics. 2008;364(1):21-26.
- [85] Seidenberger T, Siepmann J, Bley H, Maeder K, Siepmann F. Simultaneous controlled vitamin release from multiparticulates: Theory and experiment. International journal of pharmaceutics. 2011;412(1-2):68-76.
- [86] Bajpai SK, Sharma S. Dynamic release of riboflavin from ethyl cellulose coated barium alginate beads for

gastrointestinal drug delivery: an in vitro study. *Journal of Macromolecular Science, Part A: Pure and Applied Chemistry*. 2005;42(5): 649-661.7

[87] Stops F, Fell JT, Collett JH, Martini LG. Floating dosage forms to prolong gastro-retention—The characterisation of calcium alginate beads. *International journal of pharmaceutics*, 2008;350(1-2): 301-311.

[88] Kaygusuz H, Uysal M, Adımcılar V, Erim FB. Natural alginate biopolymer montmorillonite clay composites for vitamin B2 delivery. *Journal of Bioactive and Compatible Polymers*. 2015;30(1):48-56.

[89] Yang L, Shi J, Zhou X, Cao S. Hierarchically organization of biomineralized alginate beads for dual stimuli-responsive drug delivery. *International journal of biological macromolecules*. 2015;73:1-8.

[90] Carlan IC, Estevinho BN, Rocha F. Production of vitamin B1 microparticles by a spray drying process using different biopolymers as wall materials. *The Canadian Journal of Chemical Engineering*. 2020;98(8):1682-1695.

[91] Peretz S, Regev O. Carbon nanotubes as nanocarriers in medicine. *Current Opinion in colloid & interface science*. 2012;17(6):360-368.

[92] Hua J, Wang Z, Xu L, Wang X, Zhao J, Li F. Preparation polystyrene/ multiwalled carbon nanotubes nanocomposites by copolymerization of styrene and styryl-functionalized multiwalled carbon nanotubes. *Materials Chemistry and Physics*. 2013;137(3):694-698.

[93] Othman RN, Wilkinson AN. Carbon nanotube hybrids and their polymer nanocomposites. In *Synthesis, Technology and Applications of Carbon Nanomaterials*. 2019;29-60. Elsevier.

[94] Mallakpour S, Soltanian S. Morphology and thermal properties of nanocomposites based on chiral poly (ester-imide) matrix reinforced by vitamin B1 functionalized multiwalled carbon nanotubes. *Journal of Composite Materials*. 2017;51(16):2291-2300.

[95] Asghari, S, Rezaei Z, Mahmoudifard M. Electrospun nanofibers: A promising horizon toward the detection and treatment of cancer. *Analyst*. 2020; 145(8):2854-2872.

[96] Pal K, Roy S, Parida PK, Dutta A, Bardhan S, Das S, Karmakar P. Folic acid conjugated curcumin loaded biopolymeric gum acacia microsphere for triple negative breast cancer therapy in in vitro and in vivo model. *Materials Science and Engineering: C*. 2019;95:204-216.

[97] Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. *Nature nanotechnology*. 2007;2(12):751-760.

[98] Alwarappan S, Erdem A, Liu C, Li CZ. Probing the electrochemical properties of graphene nanosheets for biosensing applications. *The Journal of Physical Chemistry C*. 2009;113(20): 8853-8857.

[99] Kumar A, Lale SV, Alex MA, Choudhary V, Koul V. Folic acid and trastuzumab conjugated redox responsive random multiblock copolymeric nanocarriers for breast cancer therapy: In-vitro and in-vivo studies. *Colloids and Surfaces B: Biointerfaces*. 2017;149:369-378.

[100] Yang, G., Wang, J., Wang, Y., Li, L., Guo, X., & Zhou, S. (2015). An implantable active-targeting micelle-in-nanofiber device for efficient and safe cancer therapy. *ACS nano*. 9(2), 1161-1174.

[101] Poltavets YI, Zhirnik AS, Zavarzina VV, Semochkina YP,

Shuvatova VG, Krashennnikova AA, Posypanova GA. In vitro anticancer activity of folate-modified docetaxel-loaded PLGA nanoparticles against drug-sensitive and multidrug-resistant cancer cells. *Cancer Nanotechnology*. 2019;10(1):1-17.

[102] Ngo CL, Le QT, Ngo TT, Nguyen DN, Vu MT. Surface modification and functionalization of carbon nanotube with some organic compounds. *Advances in Natural Sciences: Nanoscience and Nanotechnology*. 2013;4(3):035017.

[103] Hua J, Wang Z, Xu L, Wang X, Zhao J, Li F. Preparation polystyrene/multiwalled carbon nanotubes nanocomposites by copolymerization of styrene and styryl-functionalized multiwalled carbon nanotubes. *Materials Chemistry and Physics*. 2013;137(3):694-698.

[104] Mallakpour S, Soltanian S. Morphology and thermal properties of nanocomposites based on chiral poly (ester-imide) matrix reinforced by vitamin B1 functionalized multiwalled carbon nanotubes. *Journal of Composite Materials*. 2017;51(16):2291-2300.